Examiner:

Art Unit:

Fubara, Blessing M.

1615

APPLICANT: William J. Curatolo, et al.

SERIAL NO.: 09/742,785

FILED: December 20, 2000

FOR: Pharmaceutical Compositions

Providing Enhanced Drug Concentrations

Commissioner for Patents Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.131

- I, Douglas A. Lorenz, declare that:
- 1. This declaration is to establish completion of the invention of this application in the United States at a date prior to November 23, 1999, that is the effective date of U.S. Published Patent Application 2003/0215496 that was cited by the examiner, and to establish completion of the invention of this application in the United States at a date prior to February 9, 1999, that is the effective date of U.S. Patent 6,548,555 B1, also cited by the examiner.
- 2. I am one of the inventors of the instant application.
- 3. To establish the date of completion of the invention of this application, reproductions of notebook entries are submitted as evidence as Exhibit A. The actual dates in the notebook entries have been redacted.

- 4. From these documents it can be seen that the invention in this application was made in the United States at least by the date of February 9, 1999, which is a date earlier than the effective date of the reference.
- 5. In particular attached to this declaration are notebook pages related to work I supervised. These pages show that the combination of a low-solubility drug in a solubility improved form combined with a concentration-enhancing polymer results in dissolved drug concentrations that are greater than the dissolved drug concentration provided by a control composition consisting of the crystalline drug alone. In particular, pages 3-6 of Exhibit A show that the use of a high solubility salt form (namely the mesylate salt) of two different drugs physically mixed (or triturated) with the polymer hydroxypropylmethyl cellulose acetate succinate provides concentration enhancement relative to the crystalline drug alone. This work was performed prior to February 9, 1999.

DECLARATION

6. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Douglas A. Lorenz

Date: 12 - 29 - 04

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-SCIENTIFIC NOTEBOOK CO. 2831 LAWRENCE AVE.
P.O. BOX 238
STEVENSVILLE, MI 49127
616-429-8285

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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches

Estimate Trends of Key Experiment(s)

Overall Hypothesis

Physical Model of Technology or Problem

Determine the beasalulity of using high energy forms of \$P-316,311 to increase the bromailability and overcome a fed/fosted effect.

Specific Study Goals

What is the key question about the hypothesis these experiments will answer?

I mitial straties

Experimental

Key Experimental Conditions

A150 assay from KEC 1:9 CP316, 311: HPMCAS-HF triturated - 1.021 mg 15 ml
20.4 mg/ml = rluon, 17.4 mg/ml = actand (95%)

1:9 (P316, 311: HPMCAS-MF tritorated - 1.057 mg 15 ml 21.1 mg/ml = theor 22.2 mg/ml = article (105%)

Results/Conclusions

Key Results: Did we strengthen or weaken the hypothesis?

Initial other were day old from [LH [perhaps evaporated slightly), Redo - looks better. See testing on later pages

Witnessed & Understood by	me,	Date	Invented by	Date redacted
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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches

Estimate Trends of Key Experiment(s)

Overall Hypothesis

Physical Model of Technology or Problem

Determine peasalulety of using ligh.
energy fours of CP316,311 to increase liveralulity and occurrence a bed/ basted effect.

Specific Study Goals

What is the key question about the hypothesis these experiments will answer?

More polymer succiny -

Experimental

Key Experimental Conditions

assays -

1:9 OPENSON CP316,311-27: HPM (AS-HF trit. 2-36 mg/10 mL 23.6 ug/line theor, 22.9 ug/ml ectual (97%)

1:9 CP316,311-27: HPMCAS-MF trit. 23.8 mg/ml then 22.8 mg/ml actual (96%)

Results/Conclusions

Key Results: Did we strengthen or weaken the hypothesis?

HBM (insoluble - Other sprays ment ok. Assey results look good.

Witnessed & Understood by me.

Date redacted Invented by

ate edacted

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From Page No. 1	
Type of experiment: Dissolution of CP-316.311 using centrings method Type of experiment: Dissolution of CP-316.311 using centrings method Drug: 2.33 mg 149 CP-316.311-27 HPMCAS.NFF dispersion 1442-137d 2.33 mg 149 CP-316.311-27 HPMCAS.NFF dispersion 1442-137d 2.33 mg 149 CP-316.31-127 HPMCAS.NFF dispersion 1442-137d 2.33 mg 149 CP-316.31-127 HPMCAS.NFF dispersion 1442-137d 2.33 mg 149 CP-316.31-127 HPMCAS.NFF dispersion 1442-137d Date Performed Tedacted Operator Recults: dispersion-C _m —65 pg/mL (PB) AUC _m =4.475 min* µg/mL 20h conc=38.3 ug/mL erinamed-C _m —55 pg/mL (PB) AUC _m =4.276 min* µg/mL 20h conc=38.3 ug/mL erinamed-C _m —55 pg/mL (PB) AUC _m =4.276 min* µg/mL 20h conc=38.3 ug/mL Terystalline C _m —75 pg/mL (PB) AUC _m =4.275 min* µg/mL 20h conc=38.3 ug/mL All work done in 37C convincible temp hox. Theoretical Chask (fine base) have done the assignment of the dispersion assignment or	
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Type of experiment: Dissolution of CP-316.311 using centrifuge method Drug: 2.35 mg 19 CP-316.311-27/HPMCAS-HF dispersion 1442-137d 2.33 mg 19 CP-316.311-27/HPMCAS-HF dispersion 1442-137d 2.33 mg crushed. crystalline CP-316.311-27 Receptor solution: 1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg, Date Performed redacted Operator KEC Notebook 1442-153 Results: dispersion-Cmar=65pg/mL (FB) AUCw=5.475 min*ng/mL 20h conc=38.3ug/mL rriturated- Cmar=59pg/mL (FB) AUCw=4.297 min*ng/mL 20h conc=38.3ug/mL crystalline Cmar=29pg/mC (Emp) AUCw=4.297 min*ng/mL 20h conc=32.5ug/mL crystalline Cmar=29pg/mC (Emp) AUCw=4.297 min*ng/mL 20h conc=32.5ug/mL Cmar=20pg/mC (Emp) AUCw=2.518 min*ng/m2 20h conc=32.5ug/mL crystalline Cm-29pg/mC (pm) AUCw=2.518 min*ng/m2 20h conc=32.5ug/mL crystalline Cm-316.311-27. Comments All work done in 370 controlled temp box. Theoretical Canax (for base) based on the assay results 1925.5ug/mL for the dispersion. 85ug/mL CP-316.311-27. 1442-153, dissolution of 119 CP-316.311-27.HPMCAS-HF spray-dried, triturated, cryst drug	
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Project No.__ Book No .__ TITLE 169 1442-169 From Page No._ tosts for CP-422,935-27: HPMCAS-MF (1:9) triturated mixture, and crystalline drug 165 Dissolution of CP-422,935 using centrifuge method Type of experiment: 1.8 mg 1:9 CP-422,935-27:HPMCAS-MF dispersion 1442-165b 1.8 mg 1:9 CP-422,935-27:HPMCAS-MF triturated 0.18 mg crushed, crystalline CP-422,935-27 1.8ml, NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg, Receptor solution: redacted Date Performed KEC 1442-169 Results: $\begin{array}{lll} \mbox{dispersion-} \ C_{max} = 58.1 \mu g/mL \ (FB) & \mbox{AUC}_{\infty} = 4.971 \ \mbox{min}^{\circ} \mu g/mL \ \ 20h \ \mbox{conc} = 48.0 \ \mbox{ug/mL} \\ \mbox{triturated-} & \mbox{$C_{max} = 56.7 \mu g/mL \ (FB)$ } \ \mbox{AUC}_{\infty} = 4.622 \ \mbox{min}^{\circ} \mu g/mL \ \ 20h \ \mbox{conc} = 33.5 \ \mbox{ug/mL} \\ \mbox{crystalline} & \mbox{$C_{max} = 14.7 \mu g/mL \ (FB)$ } \ \mbox{AUC}_{\infty} = 945 \ \mbox{min}^{\circ} \mu g/mL \ \ \mbox{$20h$ conc} = 18.9 \ \mbox{ug/mL} \\ \mbox{M conc} = 18.9 \ \mbox{$10m$ conc} =$ All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is $63.0\mu g/mL$ for the dispersion, $66.4\mu g/mL$ for the triturated mixture, and $66.3\mu g/mL$ for the crystalline CP-422,935-27. 1442-169, dissolution of 1:9 CP-422,935-27:HPMCAS-MF spray-dried, triturated, cryst. drug 80.0 [CP-422,935-0] (ug/mL) 60.0 40.0 20.0 0.0 0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 time (min) -G-1:9-MF trit (ave of 2) --- 1:9-MF disp (ave of 2) --- CP-422,935-27 (ave of 2) To Page No. Witnessed & Understood by me, Date Invented by Date redacted redacted Recorded by

Project No.___ Book No.___ 173 From Page No._ Dissolution Test - 1:9 Ett- 422 935 - CI: 11 1-10 Clarge Discoursion, Triticated mixture, plain xtulline de ug Type of experiment: Dissolution of CP-422,935 using centrifuge metho 1.8 mg 1:9 CP-422,935-27:HPMCAS-HF dispersion 1442-165a Drug: 1.8 mg 1:9 CP-422,935-27:HPMCAS-HF triturated 0.18 mg crushed, crystalline CP-422,935-27 Receptor solution 1.8mL NaTC-POPC in PBS, pH 6.5, 290 mOsm/kg, Date Performed redacted KEC 1442-173 Notebook Results: All work done in 37C controlled temp box. Theoretical Cmax (free base) based on the assay results is $61.7\mu g/mL$ for the dispersion, $63.6\mu g/mL$ for the triturated mixture, and $66.3\mu g/mL$ for the crystalline CP-422,935-27. 1442-173, dissolution of 1:9 CP-422,935-27:HPMCAS-HF spray-dried, triturated, cryst. drug 100.0 75.0 [CP-422,935-0] (ug/ml.) 50.0 25.0 0.0 10.0 30.0 50.0 80.0 40.0 time (min) -B-1:9-HF trit (ave of 2) -+- 1:9-HF disp (ave of 2) --- CP-422,935-27 (ave of 2) To Page No. Witnessed & Understood/by me. Date Dateinvented by redacted Recorded by redacted

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